Novel Taxanes/Epothilones

Grace Dy

Dr. Mark Green supported the development of novel taxanes and antimicrotubule agents during the lively debate session. He argued that a good "theory" of business in the pharmaceutical industry is to generate compounds that can improve ease, safety of administration, and efficacy of extant drugs, as exemplified by the experience with paclitaxel. Because paclitaxel is poorly soluble in water, it was developed for clinical use based on Cremophor EL/ethanol as a delivery agent (Taxol).[1] Cremophor has known associated biologic effects such as hypersensitivity reactions and neurotoxicity, which can significantly exacerbate innate taxane toxicities.[2] Moreover, micellar entrapment of paclitaxel by cremophor in the plasma compartment results in nonlinear pharmacokinetics and inhibition of intracellular transport of paclitaxel.[3,4]

Nanoparticle albumin-bound (*nab*) technology enables the delivery of insoluble drug without the need for a solvent, and thus, nab-paclitaxel (ABI-007, Abraxane) can circumvent the disadvantages of Cremophor. This is in fact borne out in a phase III study in women with metastatic breast cancer where Abraxane produced a higher overall response rate and survival benefit. Even though Abraxane was delivered at a 50% higher dose of the active agent paclitaxel compared with standard Taxol, it was generally significantly less toxic, with shorter administration time and no hypersensitivity reactions observed despite the absence of premedication.[5]

In NSCLC, a number of promising phase I/II studies of carboplatin in combination with Abraxane demonstrated antitumor activity comparable with carboplatin and standard Taxol but with less toxicity, particularly with Abraxane 100 mg/m^2 weekly regimen.[6] This led to the design of a phase III study comparing carboplatin area under the curve 6/Abraxane 100 mg/m^2 weekly versus carboplatin area under the curve 6/Taxol 200 mg/m^2 once every 21 days as first-line therapy in a one-to-one ratio among patients with advanced NSCLC. This study (NCT00540514) completed enrollment of 1052 patients in July 2009 at more than 100 sites globally and met its primary end point of disease response, which will lay the groundwork for its application for registrational approval in this patient population.[7]

Eribulin mesylate (E789) is a synthetic halichondrin B analog that is a nontaxane inhibitor of microtubule polymerization with no effect on depolymerization dynamics. In contrast to Taxol, it has a short infusion course (2–5 minutes on a day 1, 8 schedule every 3 weeks) and does not require prophylactic premedication against hypersensitivity reactions. In heavily pretreated patients with metastatic breast cancer, the tumor response seen and notable absence of severe neuropathy[8] were sufficiently encouraging to lead to two randomized phase III studies comparing eribulin against either capecitabine (NCT00337103) or chemotherapy agent of the treating physician's choice (EMBRACE study; NCT00388726), which have completed enrollment. A phase II trial of eribulin was also conducted in 41 patients with NSCLC who were previously treated with taxanes. Eligible patients were classified by taxane sensitivity based on disease progression occurring more than 90 days (TS sensitive); during therapy or less than 90 days after taxane therapy (TR resistant). There were three (15%) objective responses in 20 TS patients with median progression-free survival (PFS) of 6.3 months. Treatment was well tolerated, and enrollment is continuing on a two-stage design.[9]

The discussion on epothilones started with an overview of microtubule structure and function. Microtubules comprise α- and β tubulin heterodimers, which then polymerize and assemble in sheets to form microtubules. There are six α-tubulin and seven β-tubulin isotypes the combination of which differ among various tissues and cell types.[10] β-tubulin is essential for maintaining microtubular dynamic instability and is the binding site of multiple microtubule-targeting agents. Of particular interest is the βIII tubulin isoform, which is overexpressed in various tumor types and has been correlated with poor prognosis.[11] Its expression is up-regulated as a survival mechanism under various stress conditions such as hypoxia, hypoglycemia, or exposure to cytotoxic agents.[12] Silencing of its expression can induce sensitivity not only to taxanes and vinca alkaloids but also multiple other chemotherapy agents such as cisplatin, doxorubicin, and etoposide.[13] βIII tubulin is highly expressed in small cell, large cell neuroendocrine carcinoma, and approximately 40% of NSCLC, particularly adenocarcinomas.[14]

Ixabepilone is a semisynthetic analog of epothilone B, which shares a common pharmacophore with taxanes.[15] It binds to a different site of the tubulin molecule, which may explain its lack of complete cross-resistance with other tubulin-binding agents.[12] It is an inhibitor of multiple β-tubulin isoforms and has demonstrable preclinical activity against βIII tubulin-overexpressing lung cancer models that are resistant to taxanes and vinca alkaloids.[16] It showed promising activity as a second-line agent in a phase II study of patients with recurrent or metastatic NSCLC after failure of platinum-based regimen, approximately half of whom had been previously treated with a taxane.[17] An international randomized

Roswell Park Cancer Institute, Buffalo, New York.
Disclosure: The author declares no conflicts of interest.
Address for correspondence: Grace Dy, Roswell Park Cancer Institute, Buffalo, NY. E-mail: Grace.Dy@RoswellPark.org

ISSN: 1556-0864/10/0512-0433

phase II trial comparing carboplatin/paclitaxel versus carboplatin/ixabepilone as first-line therapy for advanced NSCLC is currently ongoing, with stratification according to βIII tubulin expression. Primary end point is PFS in the subgroup of patients with tumors that overexpress βIII tubulin as determined by immunohistochemistry (NCT0000723957).

Dr. Chandra Belani riposted by reminding the audience of the dismal fate of oral taxanes and other taxane formulations (e.g., poliglumex). He questioned if any of the novel taxanes are truly better in terms efficacy, toxicity, and cost-effectiveness, countering that the improved primary end point of objective response rate seen in the phase III study with carboplatin/weekly Abraxane is irrelevant without an improvement in PFS and OS end points and thus perhaps will not be sufficient to merit FDA approval. In the case of eribulin, he emphasized that there were no responses seen in the 21 TR patients, and median PFS in this population was only 1.2 months.[9] He summarized a published report of the typical course of patients experiencing sensory neuropathy from ixabepilone,[17] then rhetorically asked whether the description sounds better than the experience with standard paclitaxel. Moreover, from a cost-perspective, Taxol and docetaxel are relatively cheap compared with any of the novel taxanes. He presented cost estimates, using BSA assumption of 1.7 mg/m^2, of each agent per dose: Taxol 200 mg/m^2 was $1980 in contrast to Abraxane at $4919 (260 mg/m^2 dose) and Ixabepilone at $3340 (32 mg/m^2). Finally, he concluded that the FDA-approved pemetrexed-based platinum combinations have demonstrated efficacy and improved tolerability profiles in the nonsquamous subset of patients with NSCLC.[18,19] This raises the efficacy and tolerability benchmark for this patient population which will be difficult to surpass.

REFERENCES

1. Adams JD, Flora KP, Goldspiel BR, et al. Taxol: a history of pharmaceutical development and current pharmaceutical concerns. *J Natl Cancer Inst Monogr* 1993;15:141–147.
2. Gelderblom H, Verweij J, Nooter K, et al. Cremophor EL: the drawbacks and advantages of vehicle selection for drug formulation. *Eur J Cancer* 2001;37:1590–1598.
3. Sparreboom A, van Zuylen L, Brouwer E, et al. Cremophor EL-mediated alteration of paclitaxel distribution in human blood: clinical pharmacokinetic implications. *Cancer Res* 1999;59:1454–1457
4. Desai N, Trieu V, Yao Z, et al. Increased antitumor activity, intratumor paclitaxel concentrations, and endothelial cell transport of cremophor-free, albumin-bound paclitaxel, ABI-007, compared with cremophor-based paclitaxel. *Clin Cancer Res* 2006;12:1317–1324.
5. GradisharWJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol* 2005; 23:7794–7803.
6. Stroyakovsky DL, Manikhas GM, Makhson An, et al. Weekly and every-3-week nab-paclitaxel followed by carboplatin as first-line therapy is effective in patients with advanced non-small cell lung cancer: final results of a phase II study. *J Thor Oncol* 2009;4S1:PD3.4.1, S450.
7. Available at: http://www.drugs.com/clinical_trials/phase-3-trial-nsclc-meets-primary-endpoint-abraxane-compared-taxol-both-combo-carboplatin-9037.html. Accessed March 22, 2010.
8. Vahdat LT, Pruitt B, Fabian CJ, et al. Phase II study of eribulin mesylate, a halichondrin B analog, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. *J Clin Oncol* 2009;27:2954–2961.
9. Gitlitz BJ, Angela DM, Chandra BP, et al. Notable progression free survival (PFS) and disease control rate (DCR) with the halichondrin B analogue eribulin mesylate in advanced non-small cell lung cancer (NSCLC) patients (pts) previously treated with a taxane: a California Consortium/University of Pittsburgh/University of Chicago NCI/CTEP sponsored phase II trial. *J Thor Oncol* 2009;4(S1): PD3.3.6, S450.
10. Jordan MA, Wilson L. Microtubules as a target for anticancer drugs. *Nat Rev Cancer* 2004;4:253–265.
11. Seve P, Dumontet C. Is class III beta-tubulin a predictive factor in patients receiving tubulin-binding agents? *Lancet Oncol* 2008;9:168–175.
12. Lee FY, Smykla R, Johnston K, et al. Preclinical efficacy spectrum and pharmacokinetics of ixabepilone. *Cancer Chemother Pharmacol* 2009; 63:201–212.
13. Gan PP, Pasquier E, Kavallaris M. Class III β-tubulin mediates sensitivity to chemotherapeutic drugs in non-small cell lung cancer. *Cancer Res* 2007;67:9356–9363.
14. Katsetos CD, Kontogeorgos G, Geddes JF, et al. Differential distribution of the neuron-associated class III beta-tubulin in neuroendocrine lung tumors. *Arch Pathol Lab Med* 2000;124:535–544.
15. Giannakakou P, Gussio R, Nogales E, et al. A common pharmacophore for epothilone and taxanes: molecular basis for drug resistance conferred by tubulin mutations in human cancer cells. *Proc Natl Acad Sci USA* 2000;97:2904–2909.
16. Dumontet C, Jordan MA, Lee FY. Ixabepilone: targeting βIII-tubulin expression in taxane-resistant malignancies. *Mol Cancer Ther* 2009;8: 17–25.
17. Vansteenkiste J, Lara PN Jr, Le Chevalier T, et al. Phase II clinical trial of the epothilone B analog, Ixabepilone, in patients with non–small-cell lung cancer whose tumors have failed first-line platinum-based chemotherapy. *J Clin Oncol* 2007;25:3448–3455.
18. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol* 2008;26:3543–3551.
19. Scagliotti G, Hanna N, Fossella F, et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two phase III studies. *Oncologist* 2009;24:253–263.

